II. REMARKS

A. Status of the Claims

Claims 4-11, 15-22, 24-38, 40-48, and 52-54 were pending in the case at the time of the Office Action, with claims 4-11, 16, 18, 20-22, 25-37, 41-48, 52, and 53 having been previously withdrawn from consideration. Claims 1-3, 12-14, 23, 25, 39, and 49-51 have been canceled without prejudice or disclaimer. Claims 15, 17, 19, and 38 have been amended in the Amendment set forth herein. New claims 55-62 are added. Therefore, claims 15, 17, 19, 24, 38, 40, and 54-62 are currently under consideration. Support for the amendments to the claims and new claims is discussed below.

B. The Rejections Under 35 U.S.C. §112 Are Overcome

Claims 15, 17, 19, 23-25, 38, 50, 50-51, and 54 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the intramyocardial delivery of autologous or allogeneic mesenchymal stem cells modified *ex vivo* to express an angiogenic factor, to normal tissue adjacent to ischemic tissue in the myocardium, is said to not reasonably provide enablement for the absence of a transgene. Applicant respectfully traverses.

The Examiner argues that the specification is enabled for autologous and allogeneic transplantation, but not for xenogeneic transplantation. Without conceding that the Examiner is correct, Applicants note that the claims have been amended to pertain to methods of stimulating collateral blood vessel formation (claim 15), inducing angiogenesis (claim 17), improving contractile function (claim 19), and treating ischemia (claim 38) in ***human*** subjects using ***human*** bone marrow stromal cells. Therefore, because the methods pertain to transplantation of human cells into a human subject, the methods as written exclude xenogeneic transplantation.

Applicants reserve the right to pursue claims involving xenogeneic transplantation of bone marrow stromal cells in a continuation or divisional application.

The Examiner further argues that the claims encompass any *ex vivo* modification, which is said to be broader than *ex vivo* modification involving transformation to express an angiogenic factor. Applicant disagrees. Nevertheless, in an effort to expedite prosecution of commercially valuable subject matter, Applicant has amended the claims to make it even more clear that the *ex vivo* modification pertains to transformation to express an angiogenic transgene. Each of independent claims 15, 17, 19, and 38 have been amended to recite that the bone marrow stromal cells are "modified *ex vivo* to express a transgene encoding an angiogenic factor selected from the group consisting of ...," and to indicate that "said delivered cells express said transgene." Therefore, it is respectfully submitted that the claims as written pertain to *ex vivo* modification of cells to express a transgene encoding an angiogenic factor, and that one of ordinary skill in the art would be able to practice the claimed methods without an undue amount of experimentation.

Support for the amendments to the claims can be found generally throughout the specification, such as in the claims as originally filed. An example of support for "human subject" can be found on page 5, line 30 to page 6, line 4. An example of support for "human" bone marrow stromal cell can be found on page 9, line 17-26, and page 11, lines 24-26. An example of support for "modified *ex vivo* to express a transgene" and "wherein said delivered cells express said transgene" can be found on page 2, line 21 – page 3, line 5; page 7, line 25 – page 8, line 2, and page 8, line 27 – page 9, line 16. Support for the amendment of claims 15, 17, 19, and 38 to recite one or more of the specific transgenes can be found on page 9, lines 2-11 of the specification and originally filed claim 25.

Furthermore, new claims 55-62 are enabled by the instant specification. These claims depend from claim 15 (claims 55-56), claim 17 (claims 57-58), claim 19 (claims 59-60), and claim 38 (claims 61-62). Each of the new claims recites that the bone marrow stromal cells are autologous (claims 55, 57, 59, and 61) or allogeneic (claims 56, 58, 60, and 62). The Examiner appears to concede that these claims are enabled by the instant specification, as he writes that "other than autologous and allogeneic transplantation, no other form of transplantation is reasonably predicted to work." Office Action, page 4. Support for these new claims can be found generally throughout the specification, and in particularly on page 9, lines 17-26; page 3, lines 1-5, page 3, lines 16-21.

Applicant notes that the written description requirement has been extensively addressed by the Federal Circuit. In particular, the Federal Circuit has stated that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.'" *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ 2d 1227, 1232 (Fed. Cir. 2000). The Federal Circuit has also noted that "[if] a person or ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." *In re Alton*, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). In the instant case, Applicants' disclosure provides detail that is sufficient to establish that a person of ordinary skill in the art would have recognized that Applicant was in possession of the claimed invention, and would have recognized the presence of every limitation of the claimed invention, including use of allogeneic and autologous bone marrow stromal cells.

In view of the foregoing, it is respectfully submitted that each of claims 15, 17, 19, 23-25, 38, 50, 50-51, and 54 is enabled by the instant specification. Therefore, it is respectfully requested that the rejection of these claims under 35 U.S.C. §112, first paragraph, should be withdrawn.

C. The Rejections Under 35 U.S.C. §102(e) Are Overcome

Claims 15, 17, 19, 24, 25, 38, 40, and 54 are rejected under 35 U.S.C. §102(e) as being anticipated by Kornowski *et al.* (U.S. patent 7,097,832; hereinafter "Kornowski"). Applicants respectfully traverse this rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

In the instant case, Kornowski fails to anticipate the claimed invention because it fails to teach or suggest each limitation of the claimed invention. In particular, Kornowski fails to teach or suggest intramyocardial delivery of any human bone marrow stromal cell that has been transformed and which expresses any of the specific genes recited in the pending claims. The Examiner cites column 16, paragraph 2 as teaching modification of cells with a transgene. However, Kornowski fails to teach or suggest any of the specific transgenes recited in Applicant's claims. The Examiner makes a reference to VEGF in the Action, citing Kornowski as teaching that HIF-1 production increases VEGF production. Applicant notes, however, that the claims as written do not recite HIF-1 as a transgene, and that Kornowski does not make

reference to transformation of any cell with a transgene encoding VEGF. Therefore, because Kornowski fails to teach or suggest each limitation of the claimed invention, it fails to anticipate.

Kornowski also fails to teach or suggest use of transformed bone marrow stromal cells. The only reference to bone marrow stroma in Kornowski is a single reference to "stromal microenvironment" of bone marrow in col. 16, lines 52-58. This fails to amount teaching or suggestion in Kornowski pertaining to bone marrow stromal cells, or transformation of any bone marrow stromal cell for any of the purposes claimed.

Furthermore, none of the new claims are anticipated by Kornowski because they each depend from claims 15, 17, 19, or 38, which for the reasons discussed above are not anticipated. Applicant notes that Kornowski does not teach or suggest allogeneic transplantation of bone marrow stromal cells, as recited in new claims 56, 58, 60, and 62. Kornowski teaches administration of aspirated autologous bone marrow to a subject, and not allogeneic bone narrow. Regarding the Examples pertaining to *in vivo* administration, each pertains to use autologous bone marrow that has not been transformed. See col. 14, line 3-5, and col. 15, lines 28-30.

Applicants further note that even if Kornowski taught or suggested each of the specific transgenes recited in the pending claims, it would fail to anticipate the pending claims because its disclosure does not enable the claimed invention. "To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate." *Elan Pharm. v. Mayo Found.*, 346 F.3d 1051, 1054 (Fed. Cir. 2003). "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). *See Bristol-Myers Squibb v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374, 58 USPQ2d 1508,

1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention."); *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1566, 37 U.S.P.Q. 2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and **enable** one skilled in the art to make the anticipating subject matter." (emphasis added)). The Federal Circuit in *Elan Pharmaceuticals* explained, "It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation." *Elan Pharm.*, 346 F.3d at 1055 (citing *Minnesota Mining and Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301, 64 USPQ2d 1270, 1278 (Fed. Cir. 2002); *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1369, 52 USPQ2d 1129, 1134 (Fed. Cir. 1999)). The court indicated that the factual premises of the enablement analysis for biological processes were addressed in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In *Wands*, the court explained that a determination of whether the requisite amount of experimentation is undue may include consideration of:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id. at 737; 8 USPQ2d at 1404. *See Amgen, Inc. v. Chugai Pharm. Co.*, 727 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (discussing application of the *Wands* factors).

Based on solely the Kornowski, the *Wands* factors show it would require undue experimentation to practice the claimed invention. In view of the focus of Kornowski on use of bone marrow aspirate, and the absence of disclosure pertaining to bone marrow stromal cells and the limited discussion regarding transformation of any cell, it would require undue experimentation for one of ordinary skill in the art to practice the claimed method based on the

teaching of this reference. "Tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech v. Novo Nordisk A/S*, 108 F.3d 1361, 1366, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1996).

Therefore, it is respectfully submitted that Kornowski fails to anticipate the claimed invention. Therefore, it is respectfully requested that this rejection should be withdrawn.

D. Conclusion

In view of the foregoing, it is respectfully submitted that each of the pending claims is in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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